

CLAIMS

- Sub. B1
1. Recombinant nucleic acid containing, on the one hand a genomic sequence of an adenovirus which is defective in that it lacks the sequences needed for its replication, but which nevertheless contains those sequences which, in this genome, are the carrier of the genetic information needed for the corresponding adenovirus to enter the cells which the latter is capable of infecting, as well as the set of essential sequences needed for encapsidation of this adenovirus, and on the other hand an insert containing a nucleic acid sequence coding for a cytokine, this insert being under the control of a promoter present in or previously inserted into the abovementioned genomic sequence.
- 15 2. Recombinant nucleic acid according to claim 1, characterized in that it lacks the transactivators E1A and E1B and, where appropriate, the E3 region of the adenovirus.
- Sub B2
- 20 3. Recombinant nucleic acid according to claim 1, characterized in that the genomic sequence of the adenovirus lacks its 5' end region downstream of the early promoter of the E1A region of the adenovirus, and in that sequence coding for the cytokine is placed under the control of this early promoter.
- 25 4. Recombinant nucleic acid according to claim 1 or claim 2, characterized in that the sequence coding for the cytokine is placed under the control of an adenovirus late promoter.
5. Recombinant nucleic acid according to claim 1,

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characterized in that the genomic sequence of the adenovirus is provided with a promoter foreign to the adenovirus genome, and in that the sequence coding for the cytokine is placed under the control of this foreign promoter.

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6. Recombinant nucleic acid, characterized, either in that the insert contains sequences coding for several cytokines, or in that it contains separate inserts placed, respectively, under the control of separate promoters, which are also separate.

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7. Defective adenovirus, characterized in that it contains recombinant nucleic acid according to any one of claims 1 to 6.

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8. Culture of cells, in particular of human origin, characterized in that they are infected with the adenovirus according to claim 7.

9. Pharmaceutical composition containing the recombinant adenovirus according to claim 7, in combination with a pharmaceutically acceptable vehicle, in particular.

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10. Use of the recombinant adenovirus according to claim 7 for the preparation of antitumor drugs, preferably in a form which can be injected directly into a tumor of the host.

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11. Pharmaceutical composition containing cells according to claim 8, preferably human cells, in a state allowing them to be injected into humans.

12. Method for the production of recombinant defective adenoviruses according to claim 7,

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B2
cont.

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characterized by the transformation of transformable cell lines of higher eukaryotes (in particular of human or animal origin) themselves containing a separate nucleotide sequence capable of complementing the portion of the adenovirus genome which is lacking in the adenovirus and which would be essential for its replication, said separate sequence preferably being incorporated into the genome of the cells of said cell line, and in that the defective recombinant adenoviruses produced are recovered from the culture medium of the cells of said cell lines.

13. Method according to claim 12, characterized in that the genome of the defective adenoviruses lacks its 5' end region, and in that the cell line is a human embryonic kidney line such as line 293, which contains, integrated in its genome, a 5' end region of the genome of a type 5 adenovirus (Ad5) and having a size corresponding to approximately 11% of that of the whole genome of this adenovirus.

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